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The Emerging Role of Extracellular Vesicles Derived from Oral Bacteria in Periodontal Disease Progression and Systemic Inflammation

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Abstract

Extracellular vesicles derived from oral bacteria have recently been identified as central players in oral and systemic intercellular communication. These nanoscale particles are produced by commensal and pathogenic bacteria and carry a broad range of protein, lipid, and nucleic- acid biomolecules that can substantially affect host immune responses and surrounding/microbial response. Bacterial EVs have been shown to be involved in the pathogenesis of periodontal disease by destroying gingival tissue, affecting cytokine production transcription, and enhancing a chronic inflammatory response from the host's innate immune system through activation of the patients' pattern recognition receptor s, specifically TLRs. In addition, oral bacterial EVs can reach the bloodstream and induce systemic inflammation, providing a potential connection between periodontitis and other conditions such as atherosclerotic cardiovascular disease, diabetes, and rheumatoid arthritis. Consequently, a comprehensive understanding of oral and systemic health concepts is required to reach the full extent of these areas. It is evident that due to recent molecular research, omics technology application, and several developments in the field of nanomedicine, bacterial EVs have shown both clinical and research potential. However, the increased options for isolating EVs have led to questions surrounding potential heterogeneity and the absence of standard tests, among others. Thus, since oral bacterial EVs are re-studied to serve as biomarkers and help develop new periodontal and systemic anti-inflammatory therapies, the trends in future work will consider their newly developed research priorities.

Keywords: Extracellular vesicles; Oral bacteria; Periodontal disease; Inflammation; Toll-like receptors; Biomarkers.

1. Introduction

Periodontal disease is one of the most common chronic inflammatory disorders in humans characterized by the steady loss of teeth-supporting structures, including gingiva, periodontal ligaments, and alveolar bone (1,2,3). Traditionally, the etiology of periodontitis is linked to a symbiotic biofilm with the prevalence of Gram-negative anaerobic pathogens, such as Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia, among others. Recent data from molecular microbiology and immunopathology has uncovered a new level of microbial communication and pathogenesis—bacterial extracellular vesicles. Extracellular vesicles are nanoscale membranous particles secreted by the majority of cells, including exosomal microvesicles and apoptotic bodies, opportunistic nano-sized forms that are involved in cell-to-cell communication (4,5). Most of the EVs are within

a size range of 20 to 400 nm in lipid bilayers and are carriers of bioactive proteins, lipids, nucleic acids, and virulence factors. EVs are not only cell debris for bacteria but also vital players in intercellular communication and transporting functions. Bacteria can utilize EVs to transfer genetic materials, exchange nutrients and immune information. Moreover, they can cross the physiological barrier, which means that they can perform the function related to autophagy and communicating with other cells. Bacteria utilize EVs in the oral cavity. EVs play different functions in the oral cavity: they shape bacteria's biofilm, shift the balance between host tolerance and inflammation, and intensification the progression of either competition or cooperation (6,7). Since the composition of EVs and their number reflect the current state of producing bacteria and the environment in the microorganism, they serve as an assistant method that shows how active and how fast the bacteria operate. Extracellular vesicles from bacteria in the mouth are exceptionally critical because they can act as modulators that can initiate the immune response in a human patient (8,9). Bacteria EVs can enter epithelial barriers and disperse body-wide through systemic circulation and cause infectious diseases such as cardiovascular diseases, diabetes, and rheumatoid arthritis. Thus, oral bacterial EVs have a severe effect beyond the scope of the oral cavity, and it is linked to the systemic spreading of an infection. While oral bacteria EVs play a double role in mediating the communication between other bacterial cells and immunomodulating, it is necessary to observe the mechanisms of biogenesis, molecular compositions, and functions of the oral bacterial EVs. This study investigates recent discoveries in the oral bacterial EVs assembly, molecular-specific loads, and other influences on cells' functions and tissues. Also, we describe their impact on pathogenesis, the oral body connection, possible sharing with other bacteria, and diagnostical and therapeutical perspectives (10,11).

2. Biogenesis and Molecular Composition of Bacterial Extracellular Vesicles

Biogenesis of bacterial extracellular vesicles Bacterial extracellular vesicles (EVs) are produced through highly regulated processes, which, however, are different for Gram-negative and Gram-positive species. Gram-negative bacteria, such as Porphyromonas gingivalis and Fusobacterium nucleatum, generate EVs mostly originating from the outer membrane, commonly referred to as outer membrane vesicles . OMVs are formed when a certain section of the outer membrane bulges and is then pinched-off and released as a separate vesicle (12,13). Such pinching-off often results from shifts in the forces coupling the outer membrane and the underlying peptidoglycan layer. The above detachment results in the space between the outer membrane and the membrane of periplasm; this location is then filled with periplasmic content that gradually becomes enclosed by the budding vesicle (15,16). In contrast, Gram-positive species biogenesis of EVs seems more complicated due to their lack of the outer membrane. The thin membrane is, in turn, "surrounded by a thick peptidoglycan wall." As a result, formation of the outer membrane as a permanently extruded budding vesicle is a highly expensive procedure powered by enzymes such as autolysins or endopeptidases (16,17). The molecular content of bacterial EVs is extremely diverse, accurately reflecting the functional state of the parent cell. Generally, EVs include outer membrane proteins (OMP), lipopolysaccharides, lipoproteins, enzymes, DNA fragments, RNA species (mRNA, sRNA), as well as a variety of metabolites. They may also carry virulence factors – e.g., P. gingivalis gliase from P. gingivalis, fadA adhesin from F. nucleatum or leukotoxins from A. actinomycetemcomitans. However, like the parental cells, such EVs may modulate the behavior of the host cell, disrupt its immune signaling and, eventually, promote the destruction of connective tissue. Since lipids contribute to the stability of the vesicles and their capacity to fuse, EVs contain phospholipids such as phosphatidylethanolamine, phosphatidylglycerol and lipid A. Finally, the inclusion of sRNA into the EVs implies that bacteria can effectively differentiate between host and pathogenic gene expression (18,19).

Table 1 below summarizes the main molecular constituents of bacterial EVs and their functional significance in the context of oral and systemic pathogenesis.

Table 1. Major Molecular Components of Bacterial Extracellular Vesicles and Their Biological Roles

Component	Type	Example Molecules	Biological Function
Proteins	Structural & enzymatic	Gingipains (*P. gingivalis*), FadA (*F. nucleatum*)	Host tissue degradation, adhesion
Lipids	Membrane constituents	Phosphatidylethanolamine, Lipid A	Membrane stability, host cell interaction
Nucleic Acids	DNA, RNA	Genomic fragments, sRNA	Gene transfer, modulation of host transcription
Virulence Factors	Toxins, adhesins	Leukotoxin (*A. actinomycetemcomitans*)	Immune evasion, inflammation induction
Metabolites	Small molecules	Short-chain fatty acids	Signaling, immune modulation

3. Functional Roles of Oral Bacterial EVs in Microbial Communication

Oral bacteria use their ability to release bacterial extracellular vesicles (EVs) to control how the microflora develops and sustains itself in the mouth.HOW IT WORKS: Bacteria produce vesicles available for this kind of jobs; giving even more life to them within highly styled biofilms that Interact within small colonies and communities of thousands or tens of thousands organisms c.Many biological functions like nutrient gathering, ascending enantioselectivity coordination between bacteria that are the same species (conspecifics) and different species (heterospecifics will be involved in all these interactions between cells involved (20,21).

Extracellular vesicles as opposed to soluble signaling molecules enable the microscopic Ganx particles that are trapped inside the capsule but are not dissolved by digestive juices to flow through a variety of membranes with the guarantee that their messages will remain stable uncorrupted in a netherworld where life forms clump together and pH levels fluctuate (22,23).

Because of the mediate creation and maintenance of biofilms the EVs are essential to the transformation of large-scale microbial ecosystems. For example the organisms such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Streptococcus mutans release extracellular polysaccharides (EVs) such as adhesin proteins, EPS, and DNA fragments to increase microbial adherence or stickiness (24,25).

. In The resulting aggregates, which we refer to as biofilm is indistinguishable from these intricate two-faced lydast. Maintains gas-tight conditions, which are an intermediate between liquid and solid phase symplasts that, despite their infinite extension, maintain their own internal environment, or favourable settings for cells continuing doing their everyday activities inside this villous columinate. the EVs promote the sharing of genetic material, such as genes that confer resistance to environmental challenges or antibiotics, so that the feeder ying itself becomes sustainable (26,27).

Table 2. Functional Roles of Oral Bacterial EVs in Microbial Communication

Functional Role	Key Mechanism	Representative Species	Outcome/Effect
Biofilm formation and stabilization	Delivery of adhesins, DNA, and polysaccharides	*P. gingivalis*, *S. mutans*	Enhanced biofilm structure and antibiotic resistance
Quorum sensing modulation	Transport of signaling molecules and peptides	*F. nucleatum*, *S. gordonii*	Coordination of virulence and stress responses

Gene transfer	Packaging of plasmid or genomic DNA	*A. actinomycetemcomitans*	Spread of resistance or virulence genes
Competitive inhibition	Delivery of bacteriocins or lytic enzymes	*S. mitis*, *P. gingivalis*	Suppression of competing microbes
Cooperative signaling	Exchange of metabolic enzymes and factors	*Veillonella spp.*, *Streptococcus spp.*	Cross-feeding and metabolic synergy

4. Mechanisms of Host–EV Interaction in Periodontal Tissues

With their small size and lipid-rich membranes, bacterial extracellular vesicles (EVs) can move through mucous membranes and engage a variety of host cell types in periodontal tissue: gingival epithelial cells, fibroblasts, macrophages and dendritic cells. Intracellular vesicles must be taken up or recognized at the surface of cells, however, and have such effects. They initiate a series of molecular interactions which lead to dramatic changes in regulation of the immune response, inflammation and remodelling of tissues (28,29).

The main method by which oral bacterial EVs interact with host cells are by means of pattern recognition receptors (PRRs). These include toll-like receptors (TLRs) and NOD-like receptors (NLRs). EVs from Porphyromonas gingivalis, for example, carry lipopolysaccharides (LPS), lipoproteins and outer membrane proteins. All of these components can bind to TLR2 and TLR4, raising a signal that will lead downstream towards the activation of MAPK pathways or transcription factors like NF-κB. Therefore, pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α are released. This leads to gingival inflammation and writhing of connective tissues (Figure 1). (30,31).

In a different passive mechanism, epithelial and immune cells take in the carboxylated vesicles by endocytosis. Inside the cell, vesicles will discharge their contents—enzymes, RNA or virulence factors—into the cytoplasm, which in turn regulates gene expression and changes cellular metabolism. For example, P. gingivalis extracellular vesicles have been found to interfere with autophagy and inhibit antigen presentation. At the same time they have their own host-like receptors on them that can bind to HLA molecules. These actions create an environment which allows the pathogen to evade immunity and persist within periodontal pockets (32).

Bacterial EVs cause not only localized inflammation, but also oxidative stress and activation of matrix metalloproteinases (MMPs). This leads to the breakdown of collagen and other components in the extracellular matrix. EV-associated small RNAs can also interact with host microRNAs to further modify the transcriptional responses involved in immune defense as well as tissue integrity (33).

In this considered the communication between bacterial EVs and host periodontal cells is complex. It creates the distinctive chronic inflammatory milieu of periodontal disease by combining receptor-mediated recognition, intracellular signaling, and genetic reprogramming (34)

Table 3. Mechanisms of Interaction Between Oral Bacterial EVs and Host Periodontal Cells

Mechanism	Key Components Involved	Primary Host Target	Biological Effect
PRR activation (TLR2/TLR4/NLRs)	LPS, lipoproteins, outer membrane proteins	Epithelial cells, macrophages	NF-κB/MAPK activation → cytokine release (IL-1β, IL-6, TNF-α)
Endocytosis-mediated uptake	EV membrane lipids, adhesion proteins	Gingival epithelial cells, fibroblasts	Intracellular delivery of virulence factors; immune modulation

RNA-mediated regulation	Bacterial sRNA, mRNA fragments	Host cytoplasm	Alteration of host gene expression; suppression of immune response
Oxidative stress induction	Enzymatic proteins, toxins	Fibroblasts, neutrophils	ROS production, activation of MMPs, tissue destruction
Immune evasion mechanisms	Gingipains, proteases	Antigen-presenting cells	Inhibition of autophagy and antigen presentation

5. Contribution of Bacterial EVs to Periodontal Disease Pathogenesis

In the periodontal disease the complicated process with pathogenesis linked interactions between the host immune system and the oral cavity's micro biota bacterial extracellular vesicles (EVs) are strong inducers of inflammatory processes immunological dysregulation, and tissue death. this nanosized vesicles' aggregate virulence factors can enter gingival tissues deeply causing host reactions that eventually lead to the long-term development of disease (35).

The breakdown of the epithelial barrier is one of the primary pathogenic consequences of bacterial EVs.

Porphyromonas gingivalis for instance Gingipains, lipopolysaccharides (LPS) and outer membrane proteins found in extracellular vesicles have the ability to break down the intercellular junctional proteins of the epithelium, including occludin and E-cadherin.

The disintegration allows microorganisms to enter the tissue and causes internal damage. This breach triggers an inflammatory cascade that draws neutrophils and macrophages to the infection site by producing large amounts of IL-8 and TNF-α (36,37).

Changing the immune system is one of EVs' additional significant contributions. For instance, EVs can prevent dendritic cells from presenting antigens and interfere with macrophage phagocytosis, all the while encouraging tolerance in T cells (38).

For instance, it has been demonstrated that P. gingivalis EVs increase the production of the anti-inflammatory cytokine IL-10 by infected cells. A decline in defense against germs and a transition to a chronic infection state follow this. Furthermore, the RNA molecules linked to EVs have the ability to disrupt host microRNA production, which can further alter cytokine balances and other inflammatory gene regulation (39).

Also, EVs encourage bone resorption and osteoclast development, two characteristics of advanced periodontitis. They cause alveolar bone loss and connective tissue degeneration by upregulating matrix metalloproteinase activity and activating RANKL signaling pathways. Gingival fibroblasts and endothelial cells undergo apoptosis as a result of EV-induced oxidative stress, which leads to additional tissue structural breakdown (10).

When together, these bacterial EV pathogenetic activities transform a first local infection event into a persistent inflammatory illness. Establishing them as the primary cause of periodontal disease is crucial to its onset and progression (35).

Table 4. Pathogenic Mechanisms of Bacterial EVs in Periodontal Disease

Pathogenic Mechanism	EV Components Involved	Affected Host Target	Outcome/Effect
Epithelial barrier disruption	Gingipains, LPS, outer membrane proteins	Gingival epithelial cells	Increased permeability, bacterial invasion
Immune modulation	EV RNA, LPS, heat-shock proteins	Macrophages, dendritic cells, T-cells	Cytokine imbalance, immune evasion

Oxidative stress induction	Enzymatic proteins, toxins	Fibroblasts, endothelial cells	ROS production, apoptosis
Bone resorption activation	RANKL-inducing proteins, MMPs	Osteoclast precursors	Alveolar bone destruction
Chronic inflammation maintenance	Mixed virulence cargo	Gingival tissues, immune cells	Persistent cytokine release and tissue damage

6. Systemic Dissemination of Oral EVs and Links to Chronic Inflammatory Diseases

Because of the oral bacterial extracellular vesicles (EVs) are travel through our circulatory system with amazing efficiency it hase an impact that extends beyond the boundaries of the oral cavity and spreads inflammatory conditions throughout the body.and because of their nanoscale size and lipid bi-layered structure, EVs can, at least in part, penetrate endothelial and epithelial barriers by either entering the lymphatics (the contact between the epithelium and the bloodstream) or the plasma (the interface between the bloodstream) (36).

Once dispersed throughout the body, they could potentially activate or promote chronic conditions including rheumatoid arthritis, diabetes mellitus, atherosclerosis, and even neurodegenerative diseases by communicating with distant organs (35).

The mechanisms in which EVs translocate into tissues consist of passive diffusion through disrupted mucosal barriers and active uptake by immune cells or endothelial cells. For example the EVs from Fusobacterium nucleatum and Porygonas gingivalis are detected in serum and atherosclerotic plaques indicating their ability to circulate and selectively accumulate in the blood (as will be discussed later) (36).

The vesicles contain a variety of virulence-associated molecules including outer membrane proteins, lipopolysaccharide (LPS) and gingipains which can activate the Toll-like receptors (TLRs) in endothelial cells cause inflammation that leads to endothelial dysfunction and eventually trigger the onset of thrombosis (36).

Bacterial EVs bias cytokine levels to increase insulin resistance which in turn promotes systemic inflammation in metabolic disorders like diabetes mellitus (37).

They impede the activity of insulin signaling systems by upregulating IL-6 and TNF-α.

In rheumatoid arthritis, EVs that include heat-shock proteins and bacterial RNA fragments stimulate synovial macrophages, which exacerbates joint inflammation by activating NF-κB.

There is growing evidence linking oral EVs to neuroinflammatory diseases such as Alzheimer's. EVs that include bacterial proteases and inflammatory mediators can activate microglia and damage neurons because they can breach the blood-brain barrier. For many observers, the discovery of P. gingival is-produced DNA and gingipains in the brain tissue of Alzheimer's patients all of which demonstrate systemic dispersion and detrimental effects—is a powerful confirmation (39).

Table 5. Systemic Diseases Associated with Oral Bacterial Extracellular Vesicles

Systemic Disease	Key EV-Producing Species	Mechanism of Pathogenesis	Major Effects
Atherosclerosis	*P. gingivalis*, *F. nucleatum*	Endothelial activation via TLR2/TLR4; cytokine release	Plaque formation, vascular inflammation

Diabetes mellitus	*P. gingivalis*	TNF-α/IL-6 upregulation → insulin resistance	Impaired glucose metabolism
Rheumatoid arthritis	*A. actinomycetemcomitans*, *P. gingivalis*	Synovial macrophage activation, autoantibody induction	Joint inflammation, tissue destruction
Alzheimer's disease	*P. gingivalis*	Gingipain and DNA entry into CNS; microglial activation	Neuroinflammation, neuronal loss
Adverse pregnancy outcomes	*F. nucleatum*, *P. gingivalis*	Placental inflammation via EV translocation	Preterm birth, fetal growth restriction

7. Diagnostic and Therapeutic Potential of Oral Bacterial EVs

With the discovery of bacterial extracellular vesicles, new pathways have opened up both in diagnosis and therapeutics for periodontal and other systemic diseases. Compared with their bacterial derivations, the stable structure and nanometre scale of EVs thus offer an immediate portal into the biological state of origin. As a result, research on EVs can anticipate more accurately the metabolic phase in which these vesicles were released. And their makeup of proteins, lipids, DNA, RNA and virulence factors justifies their recognizability within many microbiota of the mouth; interaction with host also affects composition, which this work uses to position them as good materials for early diagnosis and monitoring alike (40).

Diagnoses

In periodontal disease, EVs are found in saliva, gingival crevicular fluid, and even serum and their molecular signatures match those of the local microbial environment. A number of studies have now shown that higher levels of gingipain-positive EVs from P. gingivalis are associated with more severe periods. Meanwhile, the different RNA and outer membrane proteins originating EVs in saliva can separately distinguish between health and disease. This provides a large field for non-invasive diagnosis. Also, variable EV-associated cytokine levels and LPS content changes may function as prognostic markers for those systemic side effects of local inflammation associated with escalating periodontitis (41,,42).

Therapy and Prevention

Furthermore, EVs offer therapeutic potential beyond diagnosis. Engineered or inactivated EVs can be put to use as vaccines or as immunomodulatory agents. In experiments species ranging from mice to humans, non-toxic EVs originating from P. gingivalis have been shown to evoke defensive immune responses, leading to less inflammation and bone resorption in their models of periodontitis (15).

The EVs serve as nanocarriers for targeted drug delivery easily crossing biological membranes because of the perfect match between their own and organismic characteristics (2).

Neutralizing antibodies or inhibitors targeting EV components such as gingipains or LPS may also ease the implications of their virulence.to find applications for these discoveries that are relevant in clinical terms still presents a big challenge. Standardization of the methods adopted for EV isolation, quantification, and characterization is essential if scientific results are to be made reliable and reproducible. But the obstacles the oral bacterial EVs are likely to be a new frontier for fine diagnosis of diseases and fresh therapeutic intervention in oral and systemic health, in particular (41).

Table 6. Diagnostic and Therapeutic Applications of Oral Bacterial Extracellular Vesicles

Application Type	Approach	Target/Mechanism	Expected Benefit
Diagnostic biomarker	Detection of EV proteins/RNA in saliva or serum	*P. gingivalis* gingipains, EV-RNA profiles	Early and non-invasive diagnosis of periodontitis
Disease monitoring	Quantification of EV-LPS or cytokines	LPS, IL-6, TNF-α levels	Assessment of disease severity and progression
Vaccine development	Use of detoxified EVs	Attenuated virulence factors	Induction of protective immunity
Drug delivery	Engineered EV nanocarriers	Antibiotics, anti-inflammatory agents	Targeted and efficient therapeutic delivery
Neutralization therapy	Blocking EV components with antibodies	Gingipains, LPS, OM proteins	Reduction of tissue inflammation and damage

8. Current Challenges and Future Perspectives

Although many questions remain, the study of bacterial extracellular vesicles (EVs), as well as their role in both oral and systemic diseases has made some fantastic progress of late (42). But there are still some challenges that make it difficult for this line of research to be fully taken up in homogeny throughout the clinic or translationally stemmed across different experiments. These challenges are largely to do with defining the vesicles, figuring out EV isolation techniques, characterizing the changes that occur in EVs during standardisation and, at the same time, considering both the biological complexity of interactions within an oral ecosystem or beyond its boundary (43).

One of the biggest problems here is caused by the fact that EVs are not a homogenous population. Different types of bacteria, even though they may live together in a biofilm, excrete vesicles which vary in size and the latter's configuration or function. The standard isolation methods which laboratories traditionally resort to - ultracentrifugation, filtration and size-exclusion chromatography, for example - often do not differentiate between different types of vesicles or distinguish among those from bacteria infecting oral fluids indigenous among the host-derived exosomes. This lack of standardization makes it difficult to compare one study with another, and may give rise to wrong or contradictory conclusions (11,45,46).

Practical verification of the impact of EVs is another difficult task. A lot of research employs in vitro models that are unable to replicate the intricate host-microbe interactions found in vivo (47,48). Validating the true physiological functions of EVs requires the establishment of suitable animal models and/or oral microenvironmental organ-chips. Furthermore, little is known about the molecular processes that control the selective loading of cargo into vesicles and its release from the cell (49,50).

Table 7. Key Challenges and Future Research Directions in Oral Bacterial EV Studies

Research Area	Current Challenges	Future Directions
EV Isolation and Characterization	Heterogeneity and contamination with host vesicles	Develop standardized, high-purity isolation protocols
Mechanistic Understanding	Limited insight into EV cargo selection and release	Apply genetic and imaging tools to track EV formation

Functional Validation	In vitro data lacking in vivo correlation	Use animal models and organ-on-chip systems
Clinical Translation	Safety, scalability, and reproducibility issues	Develop GMP-grade EV production and clinical testing
Integrative Approaches	Fragmented data across studies	Combine omics, bioinformatics, and systems biology methods

9. Conclusion

From oral pathogens Derived, the bacterial extracellular vesicles (EVs) have become potent mediators of host microbe interactions in a broader meaning than only a localized mouth infection. They can modify immunological responses and change cellular communication and directly contribute to inflammation and damage to periodontal tissue because of their capacity to transport a variety of molecular cargo, like the proteins, nucleic acids, and lipids. As in this review discusses thre EVs are important in the local pathophysiology of periodontal disease and may serve as a conduit between oral infections and systemic inflammatory diseases like diabetes and cardiovascular disease.

The knowledge of how EVs working has very increased due to the developments in imaging technology, the molecular profiling and isolation techniques.

The field continues to face several obstacles and insufficient cargo characterisation, heterogeneity, and purification issues that impede translation to clinical practice. It appears that the next stage of research exploration will require overcoming these obstacles using standardized methodology and an integrated omics approach.

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